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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LEESER, ERICH A	
ART UNIT	PAPER NUMBER
1624	
MAIL DATE	DELIVERY MODE
08/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,711	XU ET AL.	
	Examiner	Art Unit	
	Erich A. Leeser	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11 and 19-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,7,9-11 and 19-26* is/are rejected.

7)☒ Claim(s) *3,5 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-5-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to Applicant's submission dated June 26, 2009, in which Applicant amended claims 1-2 and 4-5, and added new claim 27.

Election/Restriction

The previous Restriction Requirement dated November 16, 2007, is withdrawn.

Information Disclosure Statement

The references contained in the IDS dated December 5, 2005, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification does not enable the instant compounds to inhibit transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; treat a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous lesion using an effective amount of a compound corresponding of formula (I) or enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention:

The instant invention is drawn to coumarin-amide derivatives which allegedly are TGF-β 1 and AngII inhibitors, including methods to inhibit transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; treat a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous lesion using an effective amount of a compound corresponding of formula (I).

The state of the prior art:

The prior art at the time the invention was made tends to show the lack of understanding in the synthetic organic chemistry community as to the use, function, and relevant activity of coumarin with regards to the inhibition of transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; treatment of a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous

lesion: "Esculetin (6,7-dihydroxy-2H-1-benzopyran-2-one), a plant-derived coumarin and immunomodulator, was found to have potent bronchodilating property in carbachol-induced bronchoconstriction and also reduces mitochondrial dysfunction in neurological diseases." Mabalirajan, et al., *Esculetin Restores Mitochondrial Dysfunction and Reduces Allergic Asthma Features in Experimental Murine Model*, The J. of Immunology, 183: 2059-2067 (2009). As such, it appears that this article says that coumarin derivatives would be useful for treating diseases of the lungs or brain, but is silent with any use for these derivatives towards the inhibition of transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; treatment of a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous lesion.

The predictability in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would not necessarily recognize, with regards to therapeutic effects, whether or not the compounds of formula (I) would be useful for inhibition of transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; treatment of a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous lesion.

Amount of guidance/working examples:

Beginning on page 57 Applicant provides "Pharmacologic Experiments" ending on page 67. These examples in the specification; however, do not definitively prove that the instant compounds can be used to inhibit transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; or treat a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous lesion using an effective amount of a compound corresponding of formula (I).

The breadth of the claims:

The breadth of claims in claims 21-22 and 24 are overly broad as they do not recite specific diseases or disorders, but simply classes of diseases or disorders generally; i.e., renal disorders; cardio-cerebrovascular diseases, and cerebrovascular accidents. Claim 24 is not unduly broad as it is limited to the specific diseases: hypertension, cerebral embolism, myocardial infarction, or stroke.

The quantity of undue experimentation needed:

Since the guidance and teaching provided by the specification is insufficient to inhibit transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; or treat a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; or a tumor or pre-cancerous lesion with an effective amount of a compound of formula (I), one of ordinary skill in the art, even with a high level of skill, is unable to use the instant compounds to inhibit transforming growth factor β1 or angiotensin II (AngII) receptor

converting enzyme; or treat of a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; and a tumor or pre-cancerous lesion as claimed without undue experimentation.

The level of the skill in the art:

The level of skill in the art is high. Due to the unpredictability in the pharmaceutical art; however, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases or diseases would benefit from this activity.

Taking all of the above factors into consideration, it is not seen how one of ordinary skill in the art would be able to make and use the compounds of formula (I) to inhibit transforming growth factor β1 or angiotensin II (AngII) receptor converting enzyme; or treat a chronic renal disorder; cardio-cerebrovascular disease, including hypertension, cerebral embolism, myocardial infarction, cerebrovascular accidents, or stroke; non-insulin dependent diabetes; and a tumor or pre-cancerous lesion without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 6-7, and 9-11 are rejected under 35 USC 102(b) as being anticipated by Chinese Patent No. CN 1207392A, which teaches coumarin and coumarin-amide derivatives, include the instant compounds. Specifically, the compounds of the abstract and pages 1-2 of the reference anticipate the aforementioned claims where instant R^3 is $CONHR_9$ and R_9 is phenyl either unsubstituted or substituted with hydroxyl, alkoxy, carboxyl, nitro, halogen or SO_3H, and instant R^4-R^8 are all hydrogen. Therefore, the instant claims 1-2, 6-11, and 18 are anticipated by Chinese Patent No. CN 1207392A.

Claim Objections

Claims 3, 5, and 27 are objected to as being dependent upon rejected independent claim 1, but would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Erich A. Leeser whose telephone number is 571-272-9932. The Examiner can normally be reached Monday through Friday from 8:30 to 6:00 EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) toll-free at 866-217-9197. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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